useful in the detection of nucleic acids utilizing electron transfer mechanisms. The invention relies on electron transfer between an electron transfer moiety (ETM) present in a nucleic acid hybridization complex and an electrode. Thus, the invention utilizes an electrode with a covalently attached nucleic acid. Upon hybridization of a target sequence, a double-stranded hybridization complex is formed that contains an ETM, and detection proceeds with the input of an AC signal resulting in electron transfer between the ETM and the electrode.

It should be noted that the conductivity or redox state of the spacer used to connect the nucleic acid and the electrode (i.e. either a conductive oligomer or an insulator) does not change during the assay; rather, the spacer forms a "pathway" for the electron between the ETM and the electrode. Accordingly, covalent attachment of the nucleic acid to the electrode is an important aspect of the invention.

Claims 19-25 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

Specifically, the Examiner objects to the double use of "covalently attached" in claims 19 and 20. The claims have been amended to obviate the rejection.

The Examiner objects to the antecedent basis of "electrode" in claim 23. Claim 23 has been amended to remove the ambiguity.

The Examiner objects to claim 25 for two reasons: the use of the word "preferably" and the definition of D when g is one. The claim has been amended to recite that B-D comprises two atoms forming a bond able to conjugate with neighboring bonds. Support for this amendment is found on page 12, lines 11-14 and on page 16, lines 4-17.

Claims 19-25 are rejected under 35 U.S.C. §102(e) as being anticipated by Ribi et al., (the '568 patent).

Ribi et al. describes a system that utilizes at least four components: a substrate, a set of interdigitating electrodes, a polymerizable surfactant film that forms a crystalline structure, and at least one binding ligand ("a member of a specific binding pair").

Ribi's substrate is an insulative solid support (see column 3, line 19), and can be made of a variety of materials. Preferred embodiments utilize polystyrene (see column 4, line 36). It should be noted that polystyrene is not a conductive material, and is not used in Ribi et al. as such.

A "highly oriented polymerized surfactant film" (column 3, lines 19-20) is then added

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to the insulative substrate. This may be done covalently or non-covalently (see column 3, lines 37-41). This surfactant film is either electronically semi-conducting or variably conducting (see column 3, lines 21-22).

Binding members (i.e. for binding a target analyte) are then added to the surfactant film (sometimes also referred to in Ribi et al. as a lipid portion; see column 5, line 26). The binding members are generally added to the surfactant film by using a linker (see column 5, lines 25-56). These linkers are chosen depending on the "degree to which one wishes to perturb the electrical properties of the polymer" (see column 5, line 34-36). That is, as shown below, the mechanism of Ribi et al. relies on a change in the electromagnetic properties of the film as a result of the binding of a target analyte. Thus, Ribi et al. states that "[t]he more rigid and shorter the linker, assuming high affinity analyte binding, the greater the perturbation of the polymer upon binding of the specific binding member to its complementary member." (Column 5, lines 37-40).

In addition, this perturbation causes a change in the electrical properties of the surfactant due to the presence of dopants. These dopants (donors and acceptors) alter their orientation in response to the binding of the target analytes, thus causing the changes in the electrical properties of the film. See column 5, lines 59-64:

> The orientation of the acceptor or donor molecule (dopant) with respect to the polymer lattice will affect the polymers' net electrical characteristics. The electrical properties of the film will be affected by analyte binding where the binding event causes a change in the orientation of the dopant molecule.

Generally, Ribi et al. appears to function in the following way. Upon binding of a target analyte, the electromagnetic properties of the film change (either its electronic or optical properties; see column 3, line 26) as a result of binding of a target analyte for detection. Therefore the film is the intervening medium between the two electrodes, and changes in the film's properties serve as the basis of the assay for the presence or absence of the target analyte.

Furthermore, in order to make this work (as shown in Figure 3, column 16, lines 27-31, and column 16, line 61 to column 17, line 42 ("Electrode Protection") of Ribi et al.), the electrodes must be electrically insulated from the aqueous medium using such things as parafilm, wax, nail polish, etc., so that direct electrical contact of two interdigitating electrodes does not occur. As the Examiner will appreciate, if there is direct electrical contact of the two electrodes through the aqueous media, the presence of charge carriers in the sample would

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provide two pathways for current flow: through the solution and through the film. Presumably this would be unacceptable.

Furthermore, Ribi et al. does not outline covalent attachment of anything, much less nucleic acids, to the electrode; rather, in Ribi et al., the surfactant is attached to the insulative substrate. As will be appreciated in the art, Ribi's disclosed methods of forming electrodes on the surfaces are non-covalent methods such as "painting" the electrodes onto the substrate (see the Examples, column 27, lines 5-10) and photoresist/etching methods (see column 10, lines 17-31).

As the Examiner is aware, the law is well established that in order to anticipate a claim, the prior art must disclose "each and every element"of the claimed invention. SSIH Equipment S.A.v. U.S. Inc. Int'l. Trade Commission, 218 USPQ 678, 688 (Fed. Cir. 1983). As stated by the Federal Circuit in In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990), "[f]or a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference." (Emphasis added). See also Glaverbel Societe Anonyme v. Northlake Marketing & Supply, Inc., 33 USPQ2d 1496 (Fed. Cir. 1995).

However, Ribi et al. does not have the covalent attachment of nucleic acids to the electrode. Accordingly, the rejection is improper and should be withdrawn.

Claims 19-25 are rejected under 35 U.S.C. §103 as being obvious over Ribi et al.

As stated in M.P.E.P. §2142, a *prima facie* case of obviousness requires three basic criteria to be met. First, there must be some suggestion or motivation to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, taken alone or in combination, must teach or suggest all the claim limitations.

The applicants submit that Ribi does not provide any motivation or suggestion to practice the claimed invention. There simply is no motivation to covalently attach the nucleic acids to the electrode. In fact, Ribi et al. actually teaches away from this, as it is important to the Ribi invention that the electrodes must be electrically insulated from the aqueous medium containing the target analyte for binding to the binding member. Having the binding member directly on the electrode would not allow this electrical insulation. Thus Ribi actually teaches away from practicing the invention. As stated in M.P.E.P. §2143.01:

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> If [the] proposed modification would render the prior art invention being modified unstatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. In re Gordon, 221 USPQ 1125 (Fed. Cir. 1984).

Similarly, a reference which leads one of ordinary skill in the art away from the claimed invention cannot render the claimed invention unpatentably obvious. Dow Chemical Co. v. American Cyanamid Co., 2 USPQ 2d 1350 (Fed. Cir. 1987).

Therefore, Ribi et al. does not provide the required motivation to combine. Thus a *prima facie* case of obviousness has not been made and the rejection is improper.

Even assuming, arguendo, that the required motivation exists, Ribi et al. does not provide a reasonable expectation of success. As argued above, the attachment of the nucleic acid to the electrode does not give a reasonable expectation of success. Accordingly, a *prima facie* case of obviousness has not been made and the rejection is improper.

Finally, Ribi et al. does not teach or suggest all of the claim elements, including the covalent attachment of the nucleic acid to the electrode. Accordingly, a *prima facie* case of obviousness has not been made and the rejection is improper.

Accordingly, the rejection under 35 U.S.C. §103 should be withdrawn.

The applicants submit that the claims are now in condition for allowance and an early notification of such is respectfully solicited. If after review, the Examiner feels that there are further unresolved issues, the Examiner is invited to call the undersigned at (415) 781-1989.

Respectfully submitted,

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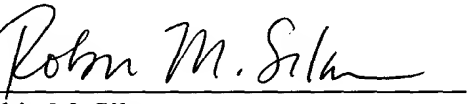
ALBRITTON & HERBERT LLP



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